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Editor's Note

Clinical Trials and the Cost of Medical Care

Government agencies, third-party payers, health maintenance organizations, professional societies, think-tanks, and probably many other organizations are concerned with the practice of "cost-effective" medicine. In a previous editorial I defined what I consider to be cost-effective medicine as diagnostic and therapeutic strategies that are the least expensive but remain "standard of practice."[1]

Randomized clinical trials seem to be the best (but not only) way to obtain evidence of efficacy and safety. Evidence-based medicine seems to be a reasonable way to practice effective medicine but may not be the least expensive.

After thinking about this for some time, I have come to the conclusion that once a clinical trial has established efficacy, the use of the drug or the procedure is generally additive to "standard treatment strategy," and therefore must cost more money, at least up front. What the cost will be over the long period of time may be another matter.

Let me illustrate what I mean by the phrase "generally additive to standard treatment strategy." There are numerous examples of clinical trials that suggest an increased initial cost plus sustained cost of the treatment.

The Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico (GISSI) clearly showed that thrombolytic therapy was better than no thrombolytic therapy during an evolving myocardial infarction (MI).

The Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) trial showed that patients with acute MI who were treated with t-PA (a more expensive drug than streptokinase) had a lower mortality than those treated with streptokinase.

The Plasminogen Activator Angioplasty Compatibility Trial (PACT) revealed that the combined use of tissue plasminogen activator and angioplasty when the blood vessel is occluded proved to be beneficial in patients with acute MI.

Asymptomatic Cardiac Ischemia Pilot Study (ACIP) results were highly suggestive that revascularization therapy was better than medical therapy for the combined events of death, MI, or need for urgent revascularization.

The Antiarrhythmics Versus Implantable Defibrillators (AVID) trial revealed a highly significant reduction in death in the implantable cardiac defibrillator (ICD) group, thus making the use of ICDs a common practice as of 1997.

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) showed that in patients with previous MI who are at high risk for ventricular tachyarrhythmia, prophylactic treatment with an implantable defibrillator leads to increased survival compared with conventional medical treatment.

The Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) revealed that amiodarone significantly reduced the incidence of ventricular fibrillation or arrhythmic death among survivors of acute MI with frequent or repetitive ventricular premature depolarization.

The European Myocardial Infarct Amiodarone Trial (EMIAT) revealed a 35% risk reduction in arrhythmic deaths but not in all-cause mortality in patients with a recent MI and left ventricular dysfunction who were receiving amiodarone. This suggested a lack of proarrhythmia in postinfarction patients and supported the use of amiodarone in patients in whom antiarrhythmic therapy is indicated.

The Chimeric 7E3 Antiplatelet Therapy in Unstable Angina Refractory to Standard Treatment (CAPTURE) trial provided evidence for beneficial effectiveness of platelet glycoprotein IIb/IIIa receptor blockade during coronary interventions, as did the Evaluation of IIb/IIIa Platelet Inhibitor for Stenting (EPISTENT) trial, which showed a reduction in death and heart attack with the use of abciximab.

Platelet Receptor Inhibition for Ischemic Syndrome Management (PRISM) revealed that tirofiban reduced ischemic events during the 48-h infusion period during which revascularization procedures were not performed, and at 30 days mortality was lowered among the patients given tirofiban.

Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) revealed that in patients with acute coronary syndromes the composite endpoint of death, MI, or recurrent angina with electrocardiographic changes prompting intervention occurred in 16.6% of patients in the enoxaparin group compared with 19.4% in the placebo group.

There have been several studies relating to the management of heart failure. The most prominent of these was the Studies of Left Ventricular Dysfunction (SOLVD) trial, in which the addition of an angiotensin-converting enzyme (ACE) inhibitor to therapy with digitalis and diuretics decreased mortality in patients with heart failure.

More recently, trials showing that beta blockers are quite effective in heart failure patients have been published. These include the Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise (PRECISE) trial. Addition of this drug to digitalis, diuretics, and an ACE inhibitor (placebo group) resulted in a significant decrease in the combined risk of morbidity and mortality. The Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA) trial also showed a

dose-dependent decrease in mortality, improvement in left ventricular ejection fraction, and a reduction in need for hospitalization. The Metoprolol CR/XL (Controlled Release) Randomized Intervention Trial in Heart Failure (MERIT-HF) revealed that metoprolol CR when added to digitalis, diuretics, and ACE inhibition resulted in decreased mortality in the metoprolol group.

Even more recently, the Randomized Aldactone Evaluation Study (RALES) showed a highly statistically beneficial reduction in mortality in patients followed for 3.5 years. Once again, this therapy was in addition to ACE inhibition, loop diuretic, and digoxin.

The Survival And Ventricular Enlargement Study (SAVE) clearly showed that patients receiving an ACE inhibitor following MI had a lower mortality than patients who did not receive an ACE inhibitor.

The Scandinavian Simvastatin Survival Study (SSSS) clearly showed a reduction in mortality in those patients with coronary artery disease (CAD) who were receiving symvastatin. Finally, the West of Scotland Coronary Prevention Study (WOSCOPS) also showed a reduction in mortality in patients at high risk for CAD who received Pravachol®.

I have not listed any clinical trials that failed to show that the addition of a drug or procedure on top of an established procedure was detrimental. There are several trials that make the point, but the classic trial that represents a "money-saving trial" is the Coronary Arrhythmia Suppression Trial (CAST), in which the use of certain antiarrhythmics after MI in patients with premature ventricular contractions proved to be detrimental. However, on balance, most trials have shown that the addition of drugs or procedures on top of established therapy improved outcome and thus are recommended in guidelines that are used in clinical practice.

I have a concern about the cost but also about the potential for drug interactions because of the number of drugs we are now pouring into our patients. For example, in heart failure, it is now fairly common practice for patients to be treated with digitalis, diuretics, an ACE inhibitor, a beta blocker, and aldactone. In some instances, hydrallazine and nitrates are added to the mixture. It is my understanding that heart failure researchers are predicting that in a few years patients will be taking seven or eight drugs for heart failure—for example, tumor necrosis factor receptor (TNFα) blocker is one therapy currently under investigation.

Another concern relates to the use of multiple drugs, several of which are hypotensive agents, in the postinfarction patient. Aspirin and beta blockers have been the mainstay of therapy for many years. However, the beta blocker studies were all completed prior to the widespread use of thrombolytic therapy or urgent angioplasty to open occluded arteries. It is now standard practice to use ACE inhibition, lipid-lowering agents, and, in instances where arrhythmias persist, amiodarone has been advised. Although not proven to be beneficial, many patients receive a nitrate. Is it necessary to continue all of these drugs indefinitely if the patient has reperfused an occluded artery and has nearly normal ventricular function? I don't know the answer to that question and I doubt that the question will be tested. My guess is that it is not necessary.

We need to reorganize our thinking somewhat about appropriate therapy for the individual patient. Instead of always adding to current therapy we need to consider stopping old therapy if the new is better, just as older diagnostic tests are discarded as a better test is devised.

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References

1. Conti CR: Can physicians practice cost-effective medicine? *Clin Cardiol* 1998;21:2–3